REMARKS

Claims 64 to 103 are under examination in the present application. By this communication, claims 82 and 97 have been amended, and new claims 104 to 136 have been added. Exhibit A presents claims 82 and 97 with markings to show the amendments made. The amendments to claims 82 and 97 are merely typographical or clerical in nature and should not be construed as amendments affecting patentability under *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) (en banc). The claims as they will stand upon entry of the amendments are presented for the Examiner's convenience in Exhibit B. Applicants respectfully request consideration of the amendments and remarks submitted herewith.

Objections to the Specification

Claim 97 has been objected to because the claim does not end in a period. In response, Applicants have provided proper punctuation for the claim and respectfully request withdrawal of the objection to claim 97.

It is asserted that there are two claims numbered "102". Applicants acknowledge with appreciation the re-numbering of the second of the two claims to number "103". Claim 103 is correctly numbered in Exhibit B, submitted herewith and therefore, Applicants respectfully request withdrawal of the objection.

Rejections Under 35 U.S.C. § 112

The rejection of claims 64 to 103 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that claim 64 is overbroad in its recitation of "[a] non-invasive method for obtaining a skin sample for use in isolating or detecting nucleic acid in a skin sample". The specification provides support for isolating all nucleic acids, in a skin sample (see page 8, lines 13 to 18). One exemplary method uses TriReagent® (Molecular Research Center, Inc., Cincinnati, OH; page 8 lines 14-16) which is, according to the manufacturer, a reagent for the isolation of total RNA or for the simultaneous isolation of RNA, DNA and proteins from biological samples. Furthermore, the specification provides ample support for detecting nucleic acid in a skin sample (see page 9, line 10 to page 13, line 4). One exemplary method for the detection of nucleic acid is polymerase chain reaction (PCR; see page 10, line 27 to page 12, line 17). Those of skill in the art recognize that PCR can detect nucleic acid in a skin sample even when the identities of the nucleic acids present are unspecified, as long as the primers in the reaction hybridize to the nucleic acid in the sample. Such hybridizable primers, *e.g.*, random primers, can be prepared using any suitable method such as conventional phosphotriester and phosphodiester methods (see page 12, lines 1 to 8). Using PCR with hybridizable primers, for example, one of skill in the art could readily detect nucleic acid of all types. Therefore, in contrast to the Examiner's assertion, the specification is enabling for the isolation and detection of any and all nucleic acids such as those encoding IL-l, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-I0, IL-12, IL-13, IL-14, factors belonging to the TGF-β superfamily, GM-CSF and interferon-γ.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, of claims 64 to 103.

The rejection of claim 66 to 69 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that no guidance is provided in the specification as to how those of skill in the art would distinguish amongst the different cellular layers of the skin. The specification provides guidance with respect to the organization of the skin layers as well as with respect to the characteristic histological appearance of the predominant cell type in each layer. The deepest layer of cells is the stratum basilis layer, composed of columnar cells (page 6, lines 17 to 18), and the layer above the stratum basilis is the stratum spinosum, which is composed of polyhedral cells (page 6, lines 18 to 19). Similarly, cells of the stratum granulosum layer, above the stratum spinosum, are flattened and contain recently-synthesized keratohyalin granules (page 6, lines 19 to 20); cells of the next layer towards the surface, the stratum lucidum are clear, without nuclei and closely packed (page 6, lines 20 to 23). Cells of the stratum corneum, the outermost layer are flattened, filled with keratin and lacking internal structures including nuclei (page 6, lines 23 to 29).

The stratiform arrangement of the skin layers, *i.e.*, the stratum corneum, the surface layer, is parallel to the stratum lucidum, which is parallel to the stratum granulosum, which is parallel to the stratum spinosum, which is parallel to the stratum basilis, allows each skin layer to be harvested separately and sequentially. Therefore the first layer to be harvested by invention methods is the outermost layer. After the outermost skin layer is harvested by invention methods, the newly exposed, next skin layer can be harvested. Thus, once the layer adjacent to the surface, the stratum corneum is harvested, the stratum lucidum can be harvested, followed by the stratum granulosum, followed by the stratum spinosum and finally, by the stratum basilis. With the histological information provided in the specification, those of skill in the art using methods known in the art, for example, microscopy methods, would readily be able to confirm the identity of the skin layer adhering to the adhesive surface. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 66 to 69 under 35 U.S.C. § 112, first paragraph.

The rejection of claim 82 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite is respectfully traversed.

It is asserted that claim 82 is indefinite because of the recitation of acronyms such as IL-4, IL-8, IL-13, and iNOS, IFN-γ. Applicants respectfully submit that those of skill in the art would recognize and understand exactly what is meant by such abbreviations. However, in order to facilitate prosecution of the application, claim 82 has been amended to include each scientific term spelled out in its entirety. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 102

The rejection of claims 64, 65, 70 to 82, 85 to 91 and 95 to 101 under 35 U.S.C. § 102 as allegedly being anticipated by Nickoloff and Naidu ((1994) *J. Am. Acad. Dermatol.*, 30:535-546) is respectfully traversed.

Applicants' invention is directed to a non-invasive method for obtaining a skin sample for use in isolating or detecting a nucleic acid in the skin sample. The method includes applying and removing at least one application of an adhesive surface to the skin such that nucleic acid adheres to the adhesive surface after its removal from the skin. Applicants invention allows the harvesting of skin and collecting of tape and nucleic acid.

In contrast, Nickoloff and Naidu merely disclose using "tape-stripping" to cause epidermal hyperplasia, *i.e.*, irritation to the skin, following which skin specimens are collected by punch biopsy. An invasive procedure such as a punch biopsy typically requires the injection of a local anesthetic so that a punch (a hollow instrument) can be firmly introduced into the skin and rotated to obtain a small cylinder without severe pain. When a large skin sample is obtained by

punch biopsy, the area may need to be closed with stitches. Nickoloff and Naidu do not disclose or suggest using tape-stripping to obtain skin samples. Indeed, by following their tape-stripping procedure with a punch biopsy procedure to obtain skin specimens, Nickoloff and Naidu teach away from obtaining skin samples using tape or any other adhesive surface. Furthermore, Nickoloff and Naidu do not teach or suggest using any non-invasive method to obtain specimen samples. Therefore, Nickoloff and Naidu cannot anticipate Applicants' invention. Accordingly, reconsideration and withdrawal of the rejection of claims 64, 65, 70 to 82, 85 to 91 and 95 to 101 under 35 U.S.C. § 102 is respectfully requested.

Rejection Under 35 U.S.C. § 103

The rejection of claims 64 to 65, 70 to 74, 76 to 82, 85 to 91, 93, 96 to 101 and 103 under 35 U.S.C. § 103(a) as being allegedly obvious over Molen *et al.* (van der Molen *et al.* (1997) *Arch. Dermatol. Res.* 289:514-518, (hereinafter "van der Molen") in view of Kondo *et al.*(1994) L*ymphokine Cytokine Res*, 13:367-375, hereinafter "Kondo") is respectfully traversed.

Applicants' invention is directed to a non-invasive method for obtaining a skin sample from which nucleic acid can be isolated or detected. The method includes applying and removing at least one application of an adhesive to the skin such that a skin sample adheres to the adhesive after its removal from the skin.

In contrast, van der Molen discloses a study related to the kinetics and penetration depth of drugs wherein tape stripping is used to remove skin cells so that the skin remaining subsequent to tape stripping can be examined using morphological and histological methods. The tape strips obtained in van der Molen were examined using X-ray microanalysis for the sole purpose of determining the distribution of skin over the tape surface to assess the efficacy of tape-stripping in removing skin from skin furrows. van der Molen does not disclose or suggest using tape-

stripping to obtain skin samples that can be used for isolation or detection of nucleic acids. Moreover, van der Molen does not disclose or suggest using the skin samples obtained by tape-stripping for any purpose other than evaluating the distribution of a marker compound in the skin. Accordingly, van der Molen does not disclose or suggest Applicants' invention.

The deficiencies of van der Molen can not be remedied by further reliance on Kondo. Kondo discloses a cytokine profile in mice ear epidermis following allergic and irritating stimuli. In Kondo, epidermis samples are obtained following animal sacrifice by dissecting the animal ears away from the animal and incubating the ears with enzyme solution for 24 hours at 4°C, after which the epidermal sheet can be peeled from the ears (page 368, column 2). Thus, Kondo discloses a tedious and invasive procedure requiring the death of the subject to obtain skin samples. Kondo does not teach or suggest using a non-invasive method to obtain skin specimens. Accordingly, Kondo does not teach or suggest Applicants' invention.

Kondo does not remedy the failures of van der Molen and van der Molen does not remedy the failures of Kondo to disclose or suggest Applicants' claimed non-invasive methods. Moreover, neither van der Molen nor Kondo provides any suggestion or motivation to combine the respective references. Accordingly, Applicants respectfully submit that neither van der Molen, nor Kondo, either separately or taken together render obvious the present invention. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

In the event any matters remain to be resolved in view of this communication, Examiner is requested to telephone Applicants' representatives Lisa A. Haile, J.D., Ph.D. at (858) 677-1456 or the undersigned, so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosures: Exhibits A and B

EXHIBIT A: CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

82. (Amended) The method of claim 79, wherein the cytokine comprises [an IL-l, an IL-2, an IL-3, an IL-4, an IL-5, an IL-6, an IL-7, an IL-8, an IL 9, an IL-IO, an IL-12, an IL-13, an IL-14] interleukin-1 (IL-l), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-10 (IL-I0), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-14 (IL-14), [a] granulocyte macrophage colony stimulating factor (GM-CSF), or an interferon, or any combination thereof.

97. (Amended) The method of claim 95, wherein the adhesive comprises an adhesive tape.